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Salvage Liver Transplantation for HCC: An Old Story without Consensus?

Gonzalo Sapisochin[1]* and Ramón Charco[2]

[1]Department of HBP Surgery & Transplantation, Hospital Universitario Vall d´Hebron, Barcelona, Spain
[2]Universidad Autónoma de Barcelona, Barcelona, Spain

Hepatocellular carcinoma (HCC), the most common liver tumor is a leading cause of mortality, accounting for more than 1 million deaths annually. Most HCC are diagnosed in association with liver cirrhosis, with the main risk factors being hepatitis B and C and alcohol abuse. In the past, HCC was diagnosed at advanced stages; no treatment could be applied and the prognosis was poor. Fortunately, as a result of screening programs in high-risk populations, patients with HCC are now diagnosed at an early stage, and up to 30% can be considered for a curative treatment. These curative treatments include liver resection (LR), liver transplantation (LT) and percutaneous ablation [1].

LT is the most effective treatment for patients with HCC since it removes the tumor and surrounding cirrhotic tissue, the main risk factor for the development of new tumors. Following the Milan criteria (single tumors ≤ 5 cm or 3 tumors all of them ≤ 3 cm), up to 75% 4-year survival has been described with a low recurrence rate (<10%) constituting the most extended criteria for LT for HCC [2]. Some groups have developed expanded criteria for LT for HCC such as the UCSF criteria and the up-to-seven criteria, with acceptable results.

Owing to organ shortage and other medical reasons, many groups have proposed LR for HCC in patients with a single tumor, preserved liver function and no portal hypertension, followed by *salvage transplantation* in the case of HCC recurrence [3]. Different results have been reported with this approach [4-6].

The main problem with this approach is the applicability of LT when HCC recurrence is diagnosed after LR. To date, low salvage transplant rates, between 16 and 25% have been reported [3-5]. Many patients with tumor recurrence exceed transplant criteria and many others are old when the tumor relapses and are therefore no longer candidates for LT. Patients with tumor recurrence outside the transplant criteria may in fact have aggressive HCC and may have had a poor prognosis even after LT. In these cases, LR offers the clear benefit of time as one can wait after LR, following up the patient and awaiting a possible recurrence. Patients with aggressive tumors will probably relapse early or in an aggressive manner, and will be excluded from LT, thereby optimizing the use of those grafts. The problem remains in the group of patients excluded because of age since, although biological age is not a formal contraindication for LT, most transplant centers have an age limit cut-off for including patients on the waiting list. This group of patients represents a lost opportunity as they could have been treated with LT and had a better long-term outcome, and at the time of recurrence only palliative treatment can be applied.

One of the first controversies addressed initially with the *salvage transplantation* approach was whether transplant surgery after a previous liver resection could impair patient outcome with regard to a higher incidence of postoperative morbidity and mortality. Thanks to improvements in surgical techniques and postoperative care, patients with *salvage transplantation* do not now present a higher incidence of postoperative morbidity and mortality, as reported in different studies [3,5]. Furthermore, with the advances in laparoscopic liver surgery, results will probably be even better and complications post-LT will be reduced [7]. Therefore, at this point, LT for patients with a previous LR for HCC should not be contraindicated, particularly in those cases in which the resection was performed with a laparoscopic approach.

In an era of organ shortage it is crucial to optimize liver grafts for LT. The strategy of *salvage transplantation* follows the premise of giving patients with transplantable HCC a chance of a cure and following up the patient for a possible HCC recurrence within transplant criteria. This approach would have several theoretical benefits. Firstly, it is well known that the main problem with LR for HCC is the high incidence of recurrence, around 70%; however there is still a chance to cure patients after LR, saving 30% of liver grafts. It is also important to note that these patients will not receive immunosuppression and, consequently, will not be exposed to its side effects.

Furthermore, much emphasis has been placed on the importance of the biological behavior of HCC [8]. After LR, and with pathological examination of the whole tumor, its differentiation, vascular invasion, satellite lesions or even molecular profiling can be evaluated. All these findings are important to establish a patient's risk of recurrence. Patients in whom factors associated with a high risk of recurrence such as microvascular invasion and/or satellitosis, particularly in poorly differentiated tumors, detected on pathological examination, should not be transplanted owing to a theoretically poor outcome. By contrast, the Barcelona Clinic Liver Cancer (BCLC) group includes patients with a high risk of recurrence post-LR on the waiting list to pre-empt tumor relapse. With this approach they describe excellent outcome after a follow-up of 55 months [9]. These results have not been validated by other groups and the number of patients in their study was very small.

A further significant point to consider is the time elapsed from LR to HCC recurrence. Early recurrence (within the first year) may indicate a group of HCC with increased aggressiveness or the existence of misdiagnosed tumors prior to LR. The poor results obtained by our group in this setting do not support LT in this group of patients, principally if HCC are poorly differentiated [3].

The main problem with *salvage transplantation* lies in the results post-transplantation compared to those of primary transplantation. In most reported series, patients with *salvage transplantation* had lower disease-free survival compared to those receiving a primary transplantation [3-4]. One possible explanation could be that patients undergoing *salvage transplantation* had been exposed to tumoral cells for a longer period. In a recent oral presentation from at the 2011 International Congress of the Liver Transplant Society (ILTS), Dr. Adam described a series of 33 patients who underwent *salvage transplantation*. This is probably the largest Western series presented to date. In his presentation, Dr. Adam confirmed his initial experience with this approach; patients who undergo *salvage transplantation*

***Corresponding author:** Gonzalo Sapisochin, Department of HBP Surgery & Transplantation, Hospital Universitario Vall d´Hebron, Barcelona, Spain, E-mail: sapisochin@me.com

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have worse outcome than those with primary transplantation. This presentation confirmed the lack of consensus for this old approach.

Finally, the best way to establish the real benefit of *salvage transplantation* for patients with transplantable HCC would be to ascertain patient survival according to the intention-to-treat principle. The time elapsed since HCC was diagnosed until death or tumor recurrence, regardless of the treatment applied (LR or LT) would have to be compared. The results would probably be better in patients who undergo primary LT.

Thus, owing to the lack of robust data, we recommend following the BCLC algorithm [1] for the treatment of cirrhotic patients with HCC.

The most important issue will be to identify which patients will do best after *salvage transplantation* and be able to select a group of patients with similar results to those primarily transplanted. Now may be the time to conduct multicenter studies with large series of patients to identify risk factors for recurrence after *salvage transplantation* and exclude high-risk patients from this approach. On the other hand, molecular markers will also be crucial in this approach to be able to optimize livers for candidates who will have benefit more from LT. Even today, controversies continue to arise regarding this extended approach to LT for HCC.

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